

### **REMARKS**

A check for the fee for a three month extension of time accompanies this response. Any fees that may be due in connection with the filing of this paper or with this application may be charged to Deposit Account No. 06-1050. If a Petition for Extension of time is needed, this paper is to be considered such Petition.

Claims 1-3, 5, 6, 8, 10-35, 37-39, 41, 42, 44, 46 and 69-95 are pending in this application. Claims 1, 5, 21, 34, 37, 39, 72, , 80 and 81 are amended to advance prosecution in order to place the application into condition for allowance. Claim 95, which is added, finds basis in claim 21. Claim 44 is cancelled without prejudice or disclaimer for prosecution in a continuing application.

The undersigned again reminds the Office that this application has undergone an extensive and long prosecution, and that, prior to departure of the previous Examiner, the application was in condition for allowance, and full faith and credit should be given to the prosecution history. It respectfully is noted that issues raised by the Examiner have been fully vetted during earlier prosecution of this application (see *e.g.*, the Office Action of February 2002 and the response thereto).

### **OBJECTION TO CLAIMS 90-93**

Claims 90-93 are objected to as being duplicative of claims 28-31. Applicant respectfully urges that the claims are of different scope. Claims 28-31 are each directed to “[a]n isolated cell;” whereas, each of claims 90-93 is directed to “[i]solated cells” [emphasis added]. Isolated *cells* are of a different scope from “an isolated cell” since the former is directed to a plurality of cells, and the latter to one or a plurality of cells. Therefore claims 90-93 are not substantial duplicates of claims 28-31.

### **OBVIOUSNESS-TYPE DOUBLE PATENTING**

Claims 1-3, 5, 6, 8, 10-35, 37-39, 41, 42, 44, 46, 69-73 and 90-94 are provisionally rejected under the judicially-created doctrine of obviousness-type double patenting over claims 1-39 and 41-51 of copending U.S. Application Serial No. 10/422,934 because claims allegedly encompass overlapping subject matter.

The propriety of an obviousness-type double patenting rejection, however, cannot be assessed until an indication that there is allowable subject matter in one of the applications. Without addressing the scope of the claims in either application, applicant concedes that there is overlap between at least one claim in the copending application and the instant application.

This is not intended as a concession regarding interpretation of the claims in either application.

Because the applications claim similar subject matter, in the event claims in the instant application are deemed allowable, applicant may not retain the overlapping or similar claims in the continuation application. Hence it is premature to file and pay for a terminal disclaimer. If the Examiner is prepared to allow the instant application, applicant will file a terminal disclaimer at that time or will take other action to obviate the rejection.

Accordingly deferral of resolution of this issue, respectfully is requested.

**THE REJECTION OF CLAIMS UNDER 35 U.S.C. 112, SECOND PARAGRAPH**

Claims 1-3, 5, 6, 8, 10-21, 23-31, 33-35, 37-39, 41, 42, 44, 46 and 69-93 are rejected under 35 U.S.C. §112, second paragraph, as allegedly indefinite because the claims fail to particularly point out and distinctly claim the subject matter on grounds discussed in turn below. Reconsideration of the grounds for this rejection is respectfully requested in view of the amendments herein and the following remarks.

**1. Claim 1**

Claim 1 is rejected vague and indefinite in the recitation of “polydactyl zinc-finger.” It is unclear how a polydactyl (many-fingered) protein could be a single “zinc-finger.” The Examiner suggests amending the claim to recite “polydactyl zinc-finger domain.” In the interest of advancing prosecution of the application, claim 1 is so-amended. It is noted that the application describes refers to a single domain as a “finger.”

Claim 1 also is rejected in the recitation of “endogenous and exogenous ligands” because it is unclear if “endogenous” refers to ligands inside the cell, those that are present in the organism or are ligands that are the physiological binding partners of a given ligand-binding domain. Endogenous ligand is a term of art understood by those of skill in the art to be the ligands for the native receptor. In reviewing the claim, the language “endogenous and exogenous ligands” is extraneous, since the claim defines the ligand specificity of the LBD to be such that “ligands that activate the fusion protein are not the ligands that activate the receptor from which the LBD was derived.”

Claim 1 is alleged to be indefinite in the recitation of “native hormone receptor” in allegedly failing to recite proper antecedent therefor. Claim 1 is amended to recite the native intracellular receptor, for which antecedent is provided in the preamble.

Claim 1 is alleged to be indefinite in the recitation of “at least about 3 nucleotides.” In the interest of advancing prosecution of the application, claim 1 is amended to recite “3 nucleotides.” This is done to advance the application to allowance, but not to concede equivalents.

**2. Claim 5**

Claim 5 is rejected as vague and indefinite in reciting “substantially activated” and “endogenous ligands relative to exogenous or non-natural ligands” because it is alleged to be unclear if “endogenous” refers to ligands inside the cell, those that are present in the organism or are ligands that are the physiological binding partners of a given ligand-binding domain and whether “exogenous or non-natural” refers to ligands that are outside the cell or are artificial or non-physiological binding partners of a given ligand-binding domain.

As amended claim 5 does not recite substantially, and defines the endogenous within its meets and bounds, thereby obviating this ground for rejection.

**3. Claim 20**

Claim 20 is vague and indefinite in reciting “a transcription regulating domain that comprises a transcription repression domain.” There is insufficient antecedent basis for this limitation, as Claim 1 only recites “the fusion protein is a ligand activated transcriptional regulator.” This rejection respectfully is traversed.

Claim 20 recites “[a] fusion protein of claim 1, *further comprising* a transcription regulating domain that comprises a transcription repression domain.” Claim 20 is clearly adding additional elements to the transcriptional regulator of claim 1. Hence there should be no antecedent in claim 1.

**4. Claim 21**

Claim 21 is rejected as indefinite in the recitation of “such as” particular combinations of elements. Claim 21 is amended to delete this inadvertent error; claim 94, which is added recites the combinations previously set forth in claim 21.

**5. Claim 34 and 37**

Claims 34 and 37 are vague and indefinite in reciting “vector is derived from” because it allegedly is unclear if vector is produced from a component of a DNA virus or a retrovirus or is a variant of a DNA virus or a retrovirus.

While not conceding the propriety of the is rejection, the claims are mended to affirmatively recite that vector is a "DNA viral vector or a retroviral vector," thereby obviating this rejection.

**6. Claims 39, 41, 42, 44 and 46**

Claims 39, 41, 42, 44 and 46 are alleged to vague and indefinite in reciting "a combination because" it is unclear "if applicant intends invention to be a physical mixture, a composition, several compositions or a kit comprising a number of compositions."

It respectfully is submitted that claims are read in light of the specification, which, in this instance, clearly describes what is intended by a combination. For example page 8, lines 20 *et seq.* state:

**Compositions, combinations and kits**

Also provided are compositions that contain the fusion proteins or the vectors that encoded the fusion proteins. Combinations of the fusion proteins or nucleic acids encoding the proteins and nucleic acid encoding a targeted gene with regulatory regions selected for activation by the fusion protein are also provided.

Compositions, particularly pharmaceutical compositions containing the fusion polypeptides in a pharmaceutically acceptable carrier are also provided.

Combinations of the expression cassette and fusion polypeptide or nucleic acid molecules, particularly expression vectors that encode the fusion polypeptide are provided. The combinations may include separate compositions or a single composition containing both elements. Kits containing the combinations and optionally instructions for administration thereof and other reagents used in preparing and administering the combinations are also provided.

Page 63, lines 20-22, states that combinations containing "a plurality of compositions" are provided. Thus, it is clear that a combination refers to as association of two components that can be separate or in a single composition. For clarity claim 39 is amended to more closely parallel the language in the specification.

**7. Claim 72**

Claim 72 is rejected as vague and definite in reciting a non-viral delivery system "wherein the non-viral delivery system is selected from the group consisting of ... direct injection of DNA, CaPO<sub>4</sub> precipitation, gene gun techniques, electroporation ...". These are all techniques for introducing DNA into cells, and are not delivery systems.

Claim 72 is amended to recite that the system includes reagents for effecting non-viral delivery, Claim 70 also is amended to provide proper antecedent for claim 72.

## **8. Claims 80 and 81**

Claims 80 and 81 are rejected vague and indefinite in reciting “wherein the second ligand binding domain is from an intracellular receptor is a nuclear hormone receptor...”. It is unclear what the metes and bounds of the claims are, as it appears that some words are omitted from the claim.

Each of claims 80 and 81 is amended to insert the missing word “that” before “is a “nuclear hormone receptor,” thereby obviating this rejection.

## **THE REJECTION OF CLAIMS UNDER 35 U.S.C. 112, FIRST PARAGRAPH - ENABLEMENT**

Claims 33-35, 37, 38, 41 and 44 are rejected under 35 U.S.C. §112, first paragraph, as failing to comply with the enablement requirement, because the specification allegedly fails to describe the claimed subject matter in such a way as to enable one skilled in the art to make and/or use the claimed subject matter. The Examiner alleges that the specification contemplates the use of the fusion proteins only within the context of gene therapy, that the art teaches that many problems remain with the use of gene transfer vectors, and that a large quantity of experimentation is necessary to determine which viral vector would be safe and effective to use for introducing a specific fusion protein into a specific tissue, organ or cell.

The Examiner urges that claims 33-35, 37 and 38 are drawn to viral vectors and that the specification contemplates the use of the fusion proteins within the context of gene therapy (page 53, lines 30 and 31 bridging page 54, lines 1-13).

The Examiner urges that there have been problems encountered during clinical uses of viral vectors in gene therapy. The Examiner cites to Kay *et al.* and other references to state that there are problems with the use of gene transfer vectors because of toxicity and immune responses, and that there is an alleged a risk of oncogenesis from retroviruses and lentiviruses. No support for these concerns are cited. The Examiner then concludes that because there have been some safety concerns that:

Due to the large quantity of experimentation necessary to determine which viral vector would be safe and effective to use for introducing a specific fusion protein into a specific tissue, organ or cell, the lack of direction/guidance presented in the specification regarding how to utilize vectors other than the adenovirus vector in a mouse model, the absence of working examples directed to the same, directed to same, the complex nature of the invention, the state of the prior art which establishes that tremendous amount of work needs to be done to improve the vectors available for gene therapy, and the breadth of the claims which fail to recite

any limitations on the vectors to be utilized, undue experimentation would be required of the skilled artisan to make and/or use the claimed invention in its full scope.

The Examiner continues regarding the uncertainties of gene therapy. The Examiner does note the extensive teachings in the application regarding how to make the constructs and vectors and the application includes data using a viral vector in an art recognized therapeutic model. The Examiner states that:

The specification teaches “the fusion proteins are administered either as a protein or as a nucleic acid encoding the protein and delivered to cells or tissues in a mammal” (page 66, lines 12-14) for treatment of “any genetic disease, for treatment of acquired disease and any other conditions” (page 66, lines 22-24). The claim broadly recites formulation for single dosage administration, but does not place any limits on the method of administration. The working examples (Example 19, especially pages 125-128) teach that the ZFP-LBD fusion proteins can be efficiently delivered via a single method of administration, an adenovirus vector and can be expressed in sufficient amounts, both in in vitro and in vivo systems, to provide high levels of drug-dependent control of a transgene in one animal model, a mouse model (page 128, lines 7-10). However, neither the specification nor the working examples provide sufficient guidance so that one of ordinary skill in the art could make or use the “combination comprising a nucleic acid molecule comprising a sequence of nucleotides that encodes the fusion protein and a regulatable expression cassette” in a pharmaceutically acceptable excipient for single dosage administration by any method of administration in any mammalian system without undertaking undue experimentation.

Relevant literature teaches that since 1990, about 3500 patients have been treated via gene therapy and although some evidence of gene transfer has been seen, it has generally been inadequate for a meaningful clinical response (Phillips, A., J Pharm Pharmacology 53: 1169-1174, 2001, abstract). Additionally, the major challenge to gene therapy is to deliver DNA to the target tissues and to transport it to the cell nucleus to enable the required protein to be expressed (Phillips, A.; pg 1170, ¶ 1). Phillips also states that the problem with gene therapy is two-fold: 1) a system must be designed to deliver DNA to a specific target and to prevent degradation within the body, and 2) an expression system must be built into the DNA construct to allow the target cell to express the protein at therapeutic levels for the desired length of time (pg 1170, ¶ 1). Therefore, undue experimentation would be required of the skilled artisan to introduce and express the claimed nucleic acid into any cell of any organism to treat an unspecified disease. Additionally, gene therapy is unpredictable and complex wherein one skilled in the art may not necessarily be able to introduce and express the claimed nucleic acid in the cell of an organism or be able to produce the encoded protein in that cell.

Due to the large quantity of experimentation necessary to introduce and express the claimed fusion protein or nucleic acid in any cell of any organism for therapy, the lack of direction/guidance presented in the specification regarding how to introduce the claimed nucleic acid, in ways other than using adenovirus vectors, in the cell of an organism to be able produce the encoded protein, the absence of working examples other than introduction of adenovirus vector into a mouse model system, directed to same, the complex nature of the invention, the state of the prior art which establishes the unpredictability of transferring genes into an organism's cells, and the breadth of the claims which fail to recite any limitations on methods of administration and organisms to be treated, undue experimentation would be required of the skilled artisan to make and/or use the claimed invention in its full scope.

The Examiner concludes that the specification does not teach how to make and use viral vectors encoding the fusion proteins.

This rejection respectfully is traversed. The Examiner is not applying the proper standard for enablement: (1) the claims are directed to products, not to methods of gene therapy; (2) notwithstanding that, safety and efficacy are not the standards for patentability; viral vectors have been shown to effect transmittal and expression of encoded gene products, and as noted by the Examiner have been employed for gene therapy.

The arguments below establish that for enablement of pharmaceutical products, US case law and the PTO guidelines only require that one of skill in the art recognize that a product have pharmacological utility. In addition, the Examiner appears to be premising her finding of undue experimentation based upon the fact that gene therapy has, in some instances been toxic, so that it would require undue experimentation to develop a safe and efficacious vector. This is not the standard for undue experimentation. Finally, the Examiner urges, without basis, that the instantly claimed vectors only have use in gene therapy. This is **not** correct. The viral vectors can be used as expression vectors to produce the fusion proteins *in vitro* and can be used in methods of *ex vivo* gene therapy.

#### **Relevant law**

To satisfy the enablement requirement of 35 U.S.C § 112, first paragraph, the specification must teach one of skill in the art to make and use the invention without undue experimentation. Atlas Powder Co. v. E.I. DuPont de Nemours, 750 F.2d 1569, 224 USPQ 409 (1984). This requirement can be met by providing sufficient disclosure, either through illustrative examples or terminology, to teach one of skill in the art how to make and how to use the claimed subject matter without undue experimentation. This clause does not require

"a specific example of everything within the scope of a broad claim." In re Anderson, 176 USPQ 331, at 333 (CCPA 1973), emphasis in original. Rather, the requirements of § 112, first paragraph "can be fulfilled by the use of illustrative examples or by broad terminology." In re Marzocchi et al., 469 USPQ 367 (CCPA 1971)(emphasis added).

Further, because "it is manifestly impracticable for an applicant who discloses a generic invention to give an example of every species falling within it, or even to name every such species, it is sufficient if the disclosure teaches those skilled in the art what the invention is and how to practice it." In re Grimme, Keil and Schmitz, 124 USPQ 449, 502 (CCPA 1960). Thus, there is no doubt that a patentee's invention may be broader than the particular embodiment shown in the specification. A patentee not only is entitled to narrow claims particularly directed to the preferred embodiment, but also to broad claims that define the invention without a reference to specific instrumentalities. Smith v. Snow, 294 U.S. 1, 11, 24 USPQ 26, 30 (1935).

Thus, there is no requirement for disclosure of every species within a genus. Applicant is entitled to claims are commensurate in scope not only with what applicant has specifically exemplified, but commensurate in scope with that which one of skill in the art could obtain by virtue of that which the applicant has disclosed.

The inquiry with respect to scope of enablement under 35 U.S.C. §112, first paragraph, is whether it would require undue experimentation to make and use the claimed invention. A considerable amount of experimentation is permissible, particularly if it is routine experimentation. The amount of experimentation that is permissible depends upon a number of factors, which include: the quantity of experimentation necessary, the amount of direction or guidance presented, the presence or absence of working examples, the nature of the invention, the state of the prior art, the relative skill of those in the art, the predictability of the art, and the breadth of the claims. Ex parte Forman, 230 USPQ 546 (Bd. Pat. App. & Int'f 1986); see also In re Wands, 8 USPQ2d 1400 (Fed. Cir. 1988).

#### **Relevant Law and U.S. Patent & Trademark Office [USPTO] Examination Guidelines**

The USPTO has released "Guidelines for Examination of Applications for Compliance with the Utility Requirement" [guidelines, which address utility under 35 U.S.C. §101 and 35 U.S.C. §112, first paragraph] and an "Overview of Legal Precedent Governing the Utility

Requirement" [legal overview] to support the guidelines. Under section I.B.4. of these guidelines Examiners are reminded that:

they must treat as true credible statements made by an applicant or a declarant in the specification or in a declaration provided under 37 CFR §1.132, unless they can show that one of ordinary skill in the art would have a rational basis to doubt the truth of such statements.

Further, the legal overview provided by the USPTO, in section II.B.1., explains that:

[a]n applicant's assertion of utility creates a presumption of utility that will be sufficient, in most cases to satisfy the utility requirement of 35 U.S.C. §101. .... To overcome this presumption, the Examiner must establish that it is more likely than not that one of ordinary skill in the art would doubt the truth of the statement of utility. In other words, the Examiner must show that the asserted utility is not credible. [Emphasis added; see e.g., In re Langer 503 F. 2d 1380, 183 USPQ 288 (CCPA 1974)].

The legal overview goes on to explain, in section II.B.2., when an asserted utility is not "credible":

To assess credibility, the Examiner should determine if one of ordinary skill in the art would consider the assertions of the applicant to have any reasonable scientific basis. If they do, they should not be challenged as not being credible. Only where they do not [e.g., if the assertion is "incredible in view of contemporary knowledge"], should the Examiner challenge the statement as not being credible.

Thus, the Examiner must accept as true any credible statement of utility made by the Appellant and may only challenge the statement upon a showing that those of skill in the art would consider the assertion to have no reasonable scientific basis.

Further, as the Examiner also has acknowledged, there is no requirement that the utility of a pharmacologically active substance be proven by in vivo testing. In re Isaacs, 146 USPQ 193, 195 (CCPA 1965). In vitro tests can raise the presumption of in vivo utility of the claimed compounds. "A standard in vitro test may be sufficient to demonstrate pharmacological activity of a compound." Bigham v. Godtfredsen, 222 USPQ 632, 637 (Bd. Pat. App. & Int'f. 1984), see, also Nelson v. Bowler, 206 USPQ 881, 883 (CCPA 1980); and Cross v. Iizuka, 224 USPQ 739, 741 (Fed. Cir. 1985). With respect to pharmacological and therapeutic utilities, the legal overview provided by the USPTO, in section I.C., interprets Nelson v. Bowler as establishing the following:

Knowledge of the pharmacological activity of any compound is obviously beneficial to the public. It is inherently faster and easier to combat illnesses and alleviate symptoms when the medical profession is armed with an arsenal of chemicals having known pharmacological activities. Since it is crucial to provide researchers with an incentive to disclose pharmacological activities in as many compounds as possible, we conclude that adequate proof of any such activity constitutes a showing of practical utility. .... These general principles are equally applicable to situations where an applicant has claimed a process for treating a human or animal disorder. [Emphasis added.]

The legal overview addresses the analysis of "credibility" of such utilities, in section II.B.2., as follows:

Special care should be taken when assessing the credibility of an asserted therapeutic utility for a claimed invention. In such cases, a previous lack of success in treating a disease or condition, or the absence of a proven animal model for testing the effectiveness of drugs for treating a disorder in humans, should not, standing alone, serve as a basis for challenging the asserted utility under §101. (Emphasis added]

Finally, the USPTO, in its legal overview, addresses some special considerations regarding asserted therapeutic or pharmacological utilities [Section III.] stating:

The Federal courts have consistently reversed rejections by the Office asserting a lack of utility under §101 for inventions claiming a pharmacological or therapeutic utility where an applicant has provided evidence supporting such a utility. In view of this, Examiners should be particularly careful in their review of evidence provided in support of an asserted therapeutic or pharmacological utility.

Thus, where a credible pharmacological utility is asserted by an applicant, it must be assumed by the Examiner to be a true statement of utility unless the Examiner shows that one of skill in the art would find no rational scientific basis for the asserted utility. Further, it is important to distinguish "pharmacological activity" from "therapeutic activity". Pharmacological activity refers, essentially, to any biological activity. For example, a compound that is demonstrated, via in vitro or in vivo testing, to affect a biological function such as blood flow, hormone binding, enzyme operation, etc. in vivo has pharmacological activity. As described above, the court, in Nelson v. Bowler, has stated that, "Knowledge of the pharmacological activity of any compound is obviously beneficial to the public." Therefore, any pharmacological activity is practically useful.

In In re Brana 34 USPQ2d 1436, U.S. App. LEXIS 6362 (Fed. Cir. 1995) the Court has stated:

[A] specification disclosure which contains a teaching of the manner and process of making and using the invention in terms which correspond in scope to those used in describing and defining the subject matter sought to be patented must be taken as in compliance with the enabling requirement of the first paragraph of §112 unless there is reason to doubt the objective truth of the statements contained therein which must be relied on for enabling support. In re Marzocchi, 58 C.C.P.A. 1069, 439 F.2d 220, 223, 169 U.S.P.Q. (BNA) 367, 369 (WP 1971).

From this it follows that the PTO has the initial burden of challenging a presumptively correct assertion of utility in the disclosure. *Id.* at 224, 169 U.S.P.Q. (BNA) at 370. Only after the PTO provides evidence showing that one of ordinary skill in the art would reasonably doubt the asserted utility does the burden shift to the applicant to provide rebuttal evidence sufficient to convince such a person of the invention's asserted utility. See <=21> *In re Bundy*, 642 F.2d 430, 433, 209 U.S.P.Q. (BNA) 48, 51 (WP 1981). n17

The PTO has not met this initial burden. The references cited by the Board, Pazdur and Martin, n18 do not question the usefulness of any compound as an antitumor agent or provide any other evidence to cause one of skill in the art to question the asserted utility of applicants' compounds. Rather, these references merely discuss the therapeutic predictive value of in vivo murine tests -- relevant only if applicants must prove the ultimate value in humans of their asserted utility. Likewise, we do not find that the nature of applicants' invention alone would cause one of skill in the art to reasonably doubt the asserted usefulness. . . .

Taking these facts -- the nature of the invention and the PTO's proffered evidence -- into consideration we conclude that one skilled in the art would be without basis to reasonably doubt applicants' asserted utility on its face. The PTO thus has not satisfied its initial burden. Accordingly, applicants should not have been required to substantiate their presumptively correct disclosure to avoid a rejection under the first paragraph of § 112. *In re Marzocchi*, 439 F.2d at 224, 169 U.S.P.Q. (BNA) at 370.

### **The rejected claims**

The rejected claims are directed to viral vectors that encode the fusion protein and also to combination that contains a composition containing the fusion protein in a pharmaceutically acceptable excipient.

33. The vector of claim 27 that is a viral vector.

34. The vector of claim 32, wherein the viral vector is a DNA viral vector or a retroviral vector.

35. The vector of claim 34 that is selected from the group consisting of an adenoviral vector, and adeno-associated viral vector, a herpes virus vector, a vaccinia virus vector and a lentiviral vector.

37. The vector of claim 33, wherein the viral vector is a DNA viral vector or a retroviral vector.

38. The vector of claim 37 that is selected from the group consisting of an adenoviral vector, and adeno-associated viral vector, a herpes virus vector, a vaccinia virus vector and a lentiviral vector.

41. The combination of claim 39 that comprises a single composition that contains the fusion protein or nucleic acid molecule that encodes the fusion protein, and the regulatable expression cassette in a pharmaceutically acceptable excipient.

## Arguments

**(1) The standard for enablement with respect to pharmaceutical products is whether one of skill in the art would recognize that a compound had pharmacological utility; safety is not an issue for consideration of patentability of pharmaceuticals**

The Examiner alleges that gene therapy is not a routine protocol because it is not always safe. In making the rejection, the Examiner cites to numerous examples in which gene therapy has been employed, but states that there have been some toxic side effects. The standard for enablement is pharmacological utility, not clinical efficacy and safety. As discussed below and above in the relevant case law, US law does not require a showing of safety and efficacy as required by the FDA, but that one of skill in the art would recognize that a particular compound, in this instance, a viral vector encoding the fusion protein, would have pharmacological utility. As discussed below in (2), the specification demonstrates that the viral vectors deliver the encoded fusion protein, which functions as a ligand activated transcriptional activator *in vivo*. Furthermore, while toxic effects have been observed with gene therapy, gene therapy does work *in vivo*. In addition, the Examiner cites to portions of the specification that teaches how to make the viral vectors, recognizes that numerous vectors are known and the specification provides working examples, demonstrating the use of a viral vector in a recognized murine model. Hence, one of skill in the art would recognize the claimed viral vectors and compositions and combinations containing the vectors as having pharmacological utility. Thus, the standard for enablement of a pharmaceutical compound is met.

The claims are directed to viral vectors that encode the fusion proteins and combinations and compositions containing the viral vectors. There is nothing in the claim the recites that the vectors are used in gene therapy (nor is a use limitation meaningful); and there is no requirement in the claim that the vector not result in undesirable side-effects in some hosts. The claims only require the vector. As discussed below with reference to the Wand's factors, one can make and use the vector *as claimed*.

Applicant respectfully submits that numerous therapeutic protocols are toxic. Chemotherapy is highly toxic; yet one does not contend that a patent application that claims a chemotherapeutic does not enable the chemotherapeutic agent.

More significantly, **Applicant respectfully submits that the question of whether the**

**instant claims satisfy the requirements of 35 U.S.C. § 112, first paragraph does not turn on the or safety and efficacy of gene therapy.** The rejected claims are directed to viral vectors that encode fusion proteins and combinations containing a fusion protein, whose construction is set forth in great detail in the specification, and a regulatable cassette containing a response element that is recognized by the nucleotide binding domain of the fusion protein, also described in similar detail in the specification. **The claims are not directed to general methods of curing disease nor to general methods of gene therapy per se.** The claims are directed to compositions and combinations containing specific components that are elucidated in great detail in the form of descriptions throughout the specification and in working examples so that they may be optimized for particular applications in gene therapy. The vectors claimed are known vectors that have been employed in gene therapy applications. The claimed vectors, compositions and combinations are uniquely recognizable as being important tools for the regulation of gene expression and would be recognized by those of skill in the art to possess pharmacological utility. Meeting standards of safety and efficacy are not required to meet the requirements for enablement (see, e.g., MPEP §2164.05, *Scott v. Finney*, 34 F.3d 1058, 1063, 32 USPQ2d 1115, 1120 (Fed. Cir. 1994), which states that the standard for enablement is not that of an established clinical regimen; and MPEP §2107.03, *In re Brana*, 51 F.3d 1560, 34 USPQ2d 1436 (Fed. Cir. 1995), discussed above, which holds that FDA approval is not a prerequisite for finding utility within the meaning of the patent laws).

Further, there is no requirement under U.S. patent law specifying particular minimum levels of optimization and certified efficacy or toxicity in order for a treatment-related area of art to qualify as sufficiently "predictable" such that lack of enablement under 35 U.S.C. § 112, first paragraph, is not a consideration. In fact, the relevant standard is not that of an established, fully optimized, clinical course of treatment; rather, even in an *unpredictable* art, a patent application satisfies the requirements of 35 U.S.C. § 112, first paragraph, as long as it provides sufficient disclosure, either through illustrative examples or terminology, to teach those of skill how to make and use the claimed subject matter with reasonable, but not undue, experimentation. There is no requirement that a treatment method achieve a specified level of efficacy or efficiency in order to be considered "enabled" by the specification. In fact, as discussed above (Relevant law), the USPTO guidelines and legal precedent clearly recognize that with respect to pharmacological and therapeutic utilities,:

Knowledge of the pharmacological activity of any compound is obviously beneficial to the public. It is inherently faster and easier to combat illnesses and alleviate symptoms when the medical profession is armed with an arsenal

of chemicals having known pharmacological activities. Since it is crucial to provide researchers with an incentive to disclose pharmacological activities in as many compounds as possible, we conclude that adequate proof of any such activity constitutes a showing of practical utility. .... These general principles are equally applicable to situations where an applicant has claimed a process for treating a human or animal disorder. [Nelson v. Bowler; Emphasis added.]

In *In re Brana*, the claims at issue, in an application filed in 1988, were directed to 5 nitrobenzodeisoquinoline 1,3 dione compounds that had anti-tumor activity. The issue was with regard to pharmaceutical inventions, what must an applicant prove to satisfy 35 U.S.C. §112, first paragraph, enablement, regarding the practical utility or usefulness of the invention for which patent protection is sought. The court stated:

The Commissioner counters that such in vivo tests in animals are only preclinical tests to determine whether a compound is suitable for processing in the second stage of testing, by which he apparently means in vivo testing in humans, and therefore are not reasonably predictive of the success of the claimed compounds for treating cancer in humans. n20 The Commissioner, as did the Board, confuses the requirements under the law for obtaining a patent with the requirements for obtaining government approval to market a particular drug for human consumption. See *Scott v. Finney*, 34 F.3d 1058, 1063, 32 U.S.P.Q.2D (BNA) 1115, 1120 (Fed. Cir. 1994) ("Testing for the full safety and effectiveness of a prosthetic device is more properly left to the Food and Drug Administration (FDA). Title 35 does not demand that such human testing occur within the confines of Patent and Trademark Office (PTO) proceedings.") . . .

Our court's predecessor has determined that proof of an alleged pharmaceutical property [\*22] for a compound by statistically significant tests with standard experimental animals is sufficient to establish utility. In *re Krimmel*, 48 C.C.P.A. 1116, 292 F.2d 948, 953, 130 U.S.P.Q. (BNA) 215, 219 (CCPA 1961); see also <=34> *In re Bergel*, 48 C.C.P.A. 1101, 292 F.2d 958, 130 U.S.P.Q. (BNA) 205 (CCPA 1961). In concluding that similar in vivo tests were adequate proof of utility the court in *In re Krimmel* stated:

We hold as we do because it is our firm conviction that one who has taught the public that a compound exhibits some desirable pharmaceutical property in a standard experimental animal has made a significant and useful contribution to the art, even though it may eventually appear that the compound is without value in the treatment in humans. *Krimmel*, 292 F.2d at 953, 130 U.S.P.Q. (BNA) at 219.

Hence, *In re Brana* and *Nelson v Bowler* and other cases establish that the patent law requires a demonstration of pharmacological utility, not clinical efficacy nor safety, to meet the standards of 35 U.S.C. §112, first paragraph. Pharmacological activity refers, essentially,

to any biological activity. For example, a compound that is demonstrated, via in vitro or in vivo testing, to affect a biological function such as blood flow, hormone binding, enzyme operation, etc. in vivo has pharmacological activity. As described above, the court, in *Nelson v. Bowler*, has stated that, "Knowledge of the pharmacological activity of any compound is obviously beneficial to the public." Therefore, ***any pharmacological activity is practically useful***. The Court in *In re Brana* applied that standard to enablement under 35 U.S.C. §112, first paragraph.

Thus, it is respectfully submitted that although methods of gene therapy may be associated with certain limitations and limited success, this does **not** establish that provision of vectors for gene therapy are not enabled because one of skill in the art would have to invent a new vector. The available vectors and methods function sufficiently such that one of skill in the art would recognize that they have pharmacological utility.

As explained above, the issue of whether the specific instant claims are enabled by the specification should not turn on the state of the art of gene therapy as generally discussed in the Office Action. Instead, the relevant question with regard to enablement of the subject matter of the instant claims is whether the particular claimed produces are described in the specification in such a way as to enable one skilled in the art to make and use the subject matter **as claimed** without undue experimentation. To establish undue experimentation a consideration of all of the "Wands factors" is warranted.

## **(2) Wands factors**

As discussed above, it is only necessary that one of skill in the art can make and use the vectors *as claimed*. The claims recite no element regarding an absence of side-effects nor regarding toxicity. There is no requirement for one of skill in the art to make and use a viral vector for gene therapy that does not have toxic side-effects, rather only that one can make and use a viral vector that one of skill in the art would recognize to have pharmacological utility.

### **(a) Scope of the rejected claims**

As discussed above, the viral vectors that encode the fusion protein and also to combination that contains a composition containing the fusion protein in a pharmaceutically acceptable excipient. The fusion proteins contain a nucleotide binding domain operatively linked to a ligand binding domain that is optionally linked operatively linked transcription regulating domain, where the nucleotide binding domain is a polydactyl zinc finger peptide

that contains at least three modular portions thereof that specifically interacts with a contiguous nucleotide sequence of at least 3 nucleotides, The combinations contain the fusion protein or a nucleic acid molecule comprising a sequence of nucleotides that encodes the fusion protein, and either (i) a regulatable expression cassette containing at least one response element recognized by the nucleic acid binding domain of the fusion protein and may also contain a gene encoding a therapeutic product; or (ii) a pharmaceutically acceptable excipient that is formulated for single dosage administration. All of the claims are directed to viral vectors, compositions and combinations that are based in specific elements, *i.e.*, a fusion protein, a regulatable expression cassette, a gene encoding a therapeutic product, and a pharmaceutically acceptable excipient; each clearly taught in the specification.

**(b) Teachings in the specification**

The specification describes in extensive detail the preparation, characterization, and isolation of the fusion proteins and preparation of viral vectors for expression thereof. The specification further provides details regarding the generation of expression cassettes containing genes encoding therapeutic products and response elements to which the nucleic acid binding domains of the claimed fusion proteins are bound. The specification further exemplifies introduction of such expression cassettes *in vitro* or *in vivo* using suitable delivery vectors, describes pharmaceutically acceptable excipients, and demonstrates *in vitro*, *in vivo* and *ex vivo* therapeutic regulation of gene expression using combinations or compositions containing exemplary fusion proteins and regulatable expression cassettes. As discussed below, numerous examples of particular fusion proteins regulating the *in vivo* and *in vitro* expression of genes encoded in exemplary expression cassettes are provided in the specification.

Applicant is entitled to claims that are commensurate in scope not only with what applicant has specifically exemplified, but commensurate in scope with that which one of skill in the art could obtain by virtue of that which the applicant has disclosed. In the above-captioned application, Applicant discloses to the public fusion proteins and compositions/combinations thereof that are stably introduced into target cells and tissue, including cells and tissue of a host animal, and are demonstrated to be capable of binding to specific response elements and regulating the expression of exemplary therapeutic genes. The compositions and combinations disclosed in the application can be manipulated and used to regulate genes encoding a therapeutic product, in target cells and tissue, including target

cells and tissue of a host animal, as is taught and specifically exemplified in the specification.

As taught in the above-captioned application, viral vectors can be used for expression of nucleic acid molecules encoding the fusion proteins. As described and exemplified in great detail in the specification, the success of any particular method for introducing the compositions and combinations into cells can be ascertained by binding assays to detect sequence specificity of the fusion protein, and by changes in gene expression that are responsive to exposure of the cells to a ligand that specifically binds to the fusion protein. The application describes and demonstrates that once the regulatable cassette and fusion protein are generated and isolated and/or introduced into cells, then any known procedure that has been performed out with any heterologous gene from any source can be employed for utilization of the claimed vectors compositions and combinations as regulators of gene expression.

The disclosure, which exemplifies particular embodiments within the scope of the claims and also teaches how one of skill in the art can obtain other embodiments within the scope of the claims. In particular, there is an enormous amount of guidance presented in the specification, there are numerous working examples, the level of skill in the art is high, and the state of the prior art at the time of filing of the application was such that a large amount of information was available concerning recombinant DNA techniques and procedures for the manipulation of DNA for the introduction of DNA encoding specific gene products into target cells and tissue, including the cells and tissue of a host animal, and expression of the encoded gene products in such cells and tissue.

**(c) Level of skill**

The level of skill in this art is recognized to be high (see, *e.g.*, Ex parte Forman, 230 USPQ 546 (Bd. Pat. App. & Int'f 1986)). The numerous articles and patents relating to established procedures for nucleic acid manipulation, transfer and expression made of record in this application, which are authored and reviewed by those of skill in the art, further evidences the high degree of skill in this art.

**(d) Presence of working examples**

The specification provides numerous working examples and descriptions of the construction and delivery of the compositions and combinations. Example 2 at page 82 of the specification shows regulation of *erbB-2* and *integrin  $\beta 3$*  (both therapeutic gene products as elaborated in the specification) by exemplary fusion constructs. Examples 4 and 19 at pages

89 and 122 of the specification, respectively, set forth in great detail the cloning strategies and the preparation of exemplary regulatable cassettes. Examples 5 and 6 beginning at page 97 of the specification provide the ligand dependent regulation of transgene expression in cells by exemplary fusion proteins, and Examples 6-8 and 16-18 beginning at page 100 and page 119, respectively, of the specification provides exemplary structural characterizations and evaluations of the correlating regulatory activity of the individual domains and the fusion protein constructs in response to endogenous and exogenous ligands. Example 19 at page 122 of the specification demonstrates the *in vivo* and *in vitro* regulation of exemplary regulatable expression cassettes using exemplary fusion proteins constructed as set forth in the various working examples and delivered using adenoviral vectors.

**(e) Knowledge of those of skill in the art**

At the time of filing of the application, a broad body of knowledge had amassed in the area of molecular biology including many technical procedures covering the manipulation of DNA and recombinant DNA techniques. Numerous such procedures are referenced in the instant application, for example, as follows:

- 1) Genetic modification of a cell can be effected using one or more techniques well known in the gene therapy field (Human Gene Therapy, April 1994, Vol. 5, p. 543-563; Mulligan, R.C. 1993).
- 2) Dual component vectors and use for gene therapy are known (see, *e.g.*, Burcin *et al.* (1999) *Proc. Natl. Acad. Sci. USA* 96: 335-360, which describes an adenovirus vector fully deleted of viral backbone genes).
- 3) Requirements for efficient gene transfer using liposomes as a delivery vehicle include (1) encapsulation of the genes of interest at high efficiency while not compromising their biological activity; (2) preferential and substantial binding to a target cell in comparison to non-target cells; (3) delivery of the aqueous contents of the vesicle to the target cell cytoplasm at high efficiency; and (4) accurate and effective expression of genetic information (Mannino, *et al.*, *Biotechniques*, 6:682, 1988). RNA, DNA and intact virions can be encapsulated within the aqueous liposome interior and be delivered to cells in a biologically active form (Fraley, *et al.*, *Trends Biochem. Sci.*, 6:77, 1981).
- 4) A method for adenovirus production is described in detail, for example, in He *et al.* (1998) *Proc. Natl. Acad. Sci. U.S.A.* 95:2509-2514. Adenovirus vector construction is described in Gorziglia *et al.* (1996) *J. Virol.* 70:4173-4178. Adenoviral vectors are well known.

5) It previously has been observed with fusion proteins containing an estrogen receptor ligand binding domain, that activity can be induced by use of not only the natural agonist estrogen (E2) but also synthetic anti-estrogens such as 4-OH tamoxifen (Littlewood *et al.* (1995) *Nucl. Acids Res.* 23:1686-1690; Danielian *et al.* (1993) *Mol. Endocrinol.* 7:234-240). The ability of the C7LBD fusion to be induced by 4-OH-tamoxifen was demonstrated.

6) In addition, numerous commercially available plasmids and patented or deposited plasmids and other well established reagents such as lipids, retroviral vectors, to prepare suitable vectors to effect gene transfer, to manipulate DNA, to prepare DNA probes and plasmids, *etc.* are provided throughout the specification.

These references to several published protocols for DNA manipulation, recombinant DNA expression, and analysis thereof demonstrate the volume of information regarding tested and reliable procedures available at the time of filing of the instant application and thus evidence the advanced state of the art at the relevant time.

#### **(f) Predictability**

The Examiner points to articles that discuss some difficulties that have been encountered in effecting gene therapy. The Examiner, however, correctly notes that gene therapy using viral vectors has been implemented. While there have been some issues, treatment has been effected. It clearly has been demonstrated, *based on actual clinical trial data*, that therapeutically relevant genes can be transferred into human patients and be expressed within the patient in such a manner as to show biologic efficacy. For example, the article Eck and Wilson (1996), cited by the previous Examiner in an earlier Office Action, provides a summary of the studies demonstrating that transfer of genes to humans is feasible (see Table 5-1, pp. 80-81) and statistics concerning the numbers and outcomes of human gene transfer studies. Eck and Wilson concludes that human gene therapy, although still in its infancy in 1996, not in 1999, the earliest effective date of claims in this application, offers the possibility for "major advancements in the prevention and treatment of many diseases". The article concludes that as "increasing numbers of investigators address these issues, better reagents likely will emerge." Contrary to the position set forth in the earlier Office Action, Eck and Wilson's assessment of the state of the art of gene therapy is that therapeutic gene transfer to humans has been proven to be feasible, as borne out by successes in gene transfer clinical trials, and its accomplishments to date at the time of publication were impressive. Another relevant article, of record in this file, is, Burcin *et al.* (1999) *Proc. Natl. Acad. Sci.*

*U.S.A.* 96:355-360, discussed above, which demonstrates the use of an adenoviral vector for *in vivo* tissue expression of a chimeric transactivator, thereby demonstrating the use of adenoviral vectors for *in vivo* gene expression. Dating back to 1992, numerous examples of effective gene therapy protocols are known. In addition, as discussed below and in the application, gene therapy protocols include *ex vivo* methods, in which a vector is introduced *ex vivo* for expression of the product. Toxicity or immunogenicity or oncogenicity or level of expression is less relevant *ex vivo*, since vector can be concentrated and used under conditions in which no replication can occur.

In fact, with respect to methods of gene therapy, the well-studied, -identified and -characterized limitations of the art, as determined through years of research and, as Eck and Wilson *et al.* report, several clinical trials, make the methods all the more predictable. The practitioner is well aware of the potential obstacles and clearly knows what he or she is up against in designing and carrying out such therapeutic methods. As such, it is respectfully submitted, that although the art of gene therapy may not have been a routine, clinical practice at the effective filing date of the subject application, it was not so unpredictable as to qualify as a major factor in the determination of whether the requirements of 35 U.S.C. § 112, first paragraph, are satisfied with respect to the instantly claimed subject matter.

Furthermore, as discussed below in (3), the vectors can be used to express the encoded fusion proteins *in vitro* and *ex vivo*. Certainly, in 1999, no one would doubt that the use of vectors for expression of proteins *in vitro* was routine and predictable.

### **Conclusion**

In summary, the specification enables one of skill in the art to, by following the methods set forth therein, construct fusion proteins and regulatable cassettes, introduce them vectors and use such vectors to express the encoded proteins. By virtue of Applicant's detailed teachings of each of the components set forth in the claimed vectors, compositions and combinations, the high level of skill in the art, the routine nature of gene expression, the breadth of the claims and the knowledge of those of skill in the art, it would not require undue experimentation, to make and use the claimed vectors, compositions and combinations, and, if necessary to combine their use with known recombinant DNA procedures, many of which are referenced in the specification, to achieve any number of particular outcomes, including the introduction and expression of nucleic acids encoding the fusion proteins for expression of therapeutic products in cells *in vitro* or *in vivo*.

Furthermore, the instant claims are **not** directed to methods of gene therapy but to viral vectors and combinations and compositions containing the vectors or fusion proteins. The standard for enablement does not require a demonstration of clinical effectiveness nor safety and efficacy (such determinations are for the FDA, not the PTO), but whether one of skill in the art would recognize that the vectors and compositions have pharmacological utility. The specification includes data demonstrating *in vivo* and *in vitro* activity; clearly sufficient to evidence that pharmacological activity of the claimed vectors and/or combinations or compositions.

Therefore, in light of the extensive teachings and examples in the specification, the high level of skill of those in this art, the knowledge of those of skill in the art, and the breadth of the claims, it would not require undue experimentation for the skilled artisan to make and use the claimed viral vectors, compositions and combinations.

**(3) The premise upon which the rejection is based is flawed.**

The Examiner urges that the only use for the viral vectors is *in vivo* gene therapy. Applicant respectfully disagrees. Viral vectors as taught in the specification can be used for methods other than gene therapy. They can be used to expression of the encoded fusion protein (see, *e.g.*, page 3, lines 1-8, page 17, lines 24-33 and page 56 of the specification) *in vitro*. In addition, the vectors can be used in *ex vivo* methods in which the protein is expressed *ex vivo* (see, *e.g.*, page 11, lines 13-29). Such methods do not require introduction of high levels of the virus nor are they limited by the amounts of virus that can be administered. Hence, whether or not gene therapy is toxic or unsafe, it is not at issue, since the claimed vectors can be employed as expression vectors to produce the fusion protein.

**(4) Fairness**

It is therefore respectfully submitted that the instant claims are commensurate in scope with the discovery and its disclosure within the above-captioned application. It would be unfair and contrary to the Constitutional mandate set forth in Article, Section 8, to deprive Applicant of claims directed to viral vectors, which as noted by the Examiner is an ultimate intended use, and indeed is an intended commercial application. To permit those of skill in the art to read the application, which teaches make and use viral vectors, combinations and compositions, but to deprive the applicant of claims directed thereto, permits those of skill in the art to practice what is disclosed, but avoid infringing the claims. This is unfair and unduly limiting and unfair.

Applicant is entitled to claims that are commensurate in scope not only with what applicant has specifically described and exemplified, but commensurate in scope with that which one of skill in the art could obtain by virtue of that which the applicant has disclosed. In this instance, applicant has disclosed and taught how to make and use viral vectors, compositions and combinations, including provision of working examples. It is unfair and unduly limiting to require applicants to limit the claims, when the application clearly teaches how to make and use the claimed products. The specification clearly places those of skill in the art in possession of viral vectors that encode the fusion proteins and compositions and combinations containing the vectors; the specification teaches how to make them and use them *in vitro* and *in vivo* to express the encoded fusion protein. To deny claims that recite viral vectors, compositions or combinations not only is unduly limiting, but is contrary to the public policy upon which the U.S. patent laws are based. See, for example, *In re Goffe*, 542 F.2d 801, 166 USPQ 85 (CCPA 1970):

for the Board to limit appellant to claims involving the specific materials disclosed in the examples so that a competitor seeking to avoid infringing the claims can merely follow the disclosure and make routine substitutions "is contrary to the purpose for which the patent system exists - to promote progress in the useful arts."

The public purpose on which the patent law rests requires the granting of claims commensurate in scope with the disclosure. This requires as much the granting of broad claims on broad inventions as it does the granting of more specific claims on more specific inventions. *In re Sus and Schafer*, 49 CCPA 1301, 306 F.2d 494, 134 USPQ 301, at 304. If applicant is required to limit the claims as suggested by the Examiner, then those of skill in the art can, by virtue of the teachings of this application, prepare viral vectors, compositions and combinations containing the vectors, and use them for expression of the encoded fusion protein., thereby practicing what is disclosed in the application, but avoid infringing specific claims directed to the vectors, combinations and compositions (they would infringe the broader independent claims) The instant application places the public in possession of the vectors, combinations and compositions. Having provided this disclosure, it permits others to benefit therefrom, and applicant is entitled to claims in return. Companies can ill-afford to dedicate any aspect of their innovations to the public.

**THE REJECTION OF CLAIMS 10, 13, 15-19 AND 21 UNDER 35 U.S.C. §112, FIRST PARAGRAPH, WRITTEN DESCRIPTION**

Claims 10, 13, 15-19 and 21 are rejected under 35 U.S.C. §112, first paragraph, because the specification allegedly fails to comply with the written description requirement, because the claims allegedly contain subject matter that was not described in the specification in such a way as to reasonably convey that the Applicant had possession of the claimed subject matter. The Examiner alleges that the specification does not provide evidence of possession of the claimed genus of fusion proteins that include variants of zinc-finger proteins, or variants of the LBD domains of the estrogen and progesterone receptor other than those disclosed on pages 106 and 125, or derivatives, multimers and combinations of VP16, VP64, TA2, STAT-6, p65 or derivatives, multimers and combinations of the transcription activation domains recited in claim 15. The Examiner alleges that the Applicant has not identified any particular portion of each of the components of the fusion protein that must be conserved and only recites that the transcription activation activity of the variants must be preserved. This rejection respectfully is traversed.

**Relevant Law**

The purpose behind the written description requirement is to ensure that the patent applicant had possession of the claimed subject matter at the time of filing of the application In re Wertheim, 541 F.2d 257, 262, 191 USPQ 90, 96 (CCPA 1976). The manner in which the specification meets the requirement is not material; it may be met by either an express or an implicit disclosure.

35 U.S.C. §112 requires a written description of the invention. This requirement is distinct from and not coterminous with the enablement requirement:

The purpose of the 'written description' requirement is broader than to merely explain how to 'make and use'; the applicant must also convey with reasonable clarity to those skilled in the art that, as of the filing date sought, he or she was in possession of the invention. The invention is, for purposes of the 'written description' inquiry, whatever is now claimed." Vas-Cath, Inc. v. Mahurkar, 935 F.2d at 1563-64, 19 USPQ2d at 1117 (emphasis in original).

The issue with respect to 35 U.S.C. §112, first paragraph, adequate written description has been stated as:

[d]oes the specification convey clearly to those skilled in the art, to whom it is addressed, in any way, the information that appellants invented that specific compound [claimed embodiment] Vas-Cath, Inc. v. Mahurkar, at

1115, quoting In re Ruschig, 390 F.2d 1990, at 995-996, 154 USPQ 118 at 123 (CCPA 1967).

A specification must convey with reasonable clarity to those skilled in the art that, as of the filing date sought, he or she was in possession of the invention, *i.e.*, whatever is now claimed. Vas-Cath, Inc. v. Mahurkar, 935 F.2d 1555, 1563-64, 19 USPQ.2d 1111, 1117 (Fed. Cir. 1991). A written description requirement issue generally involves the question of whether the subject matter of a claim is supported by or conforms to the disclosure of an application as filed. The test for sufficiency of support in a patent application is whether the disclosure of the application relied upon "reasonably conveys to the artisan that the inventor had possession at that time of the later claimed subject matter." Ralston Purina Co. v. Far-Mar-Co., Inc., 772 F.2d 1570, 1575, 227 USPQ 177, 179 (Fed. Cir. 1985) (quoting In re Kaslow, 707 F.2d 1366, 1375, 217 USPQ 1089, 1096 (Fed. Cir. 1983)) (see also, MPEP 2163.02).

An objective standard for determining compliance with the written description requirement is "does the description clearly allow persons of skill in the art to recognize that he or she invented what is claimed." In re Gosteli, 872 F.2d 1008, 1012, 10 USPQ.2d 1614, 1618 (Fed. Cir.1989).

The Examiner has the initial burden of presenting evidence or reasons why persons skilled in the art would not recognize in an applicant's disclosure a description of the invention defined by the claims. In re Wertheim, 541 F.2d 257, 265, 191 USPQ 90, 98 (CCPA 1976); *See also* Ex parte Sorenson, 3 USPQ.2d 1462, 1463 (Bd. Pat.App. & Inter. 1987). By disclosing in a patent application a device that inherently performs a function or has a property, operates according to a theory or has an advantage, a patent application necessarily discloses that function, theory or advantage, even though it says nothing explicit concerning it. The application may later be amended to recite the function, theory or advantage without introducing prohibited new matter. In re Reynolds, 443 F.2d 384, 170 USPQ 94 (CCPA 1971); and In re Smythe, 480 F. 2d 1376, 178 USPQ 279 (CCPA 1973).

Furthermore, the subject matter of the claims need not be described literally (*i.e.*, using the same terms or *in haec verba*) in order for the disclosure to satisfy the description requirement. If a claim is amended to include subject matter, limitations, or terminology not present in the application as filed, involving a departure from, addition to, or deletion from the disclosure

of the application as filed, the examiner should conclude that the claimed subject matter is not described in that application. This conclusion will result in the rejection of the claims affected under 35 U.S.C.112, first paragraph - description requirement, or denial of the benefit of the filing date of a previously filed application, as appropriate.

**The rejected claims:**

The rejected claims are as follows:

10. The fusion protein of claim 1, that comprises at least four zinc fingers or variants thereof.
13. The fusion protein of claim 3, wherein the hormone receptor is a progesterone receptor variant or an estrogen receptor variant.
15. The fusion protein of claim 2, wherein the transcription regulating domain comprises a transcription activation domain selected from the group consisting of VP16, VP64, TA2, STAT-6, p65 and derivatives, multimers and combinations thereof that have transcription activation activity.
16. The fusion protein of claim 14, wherein the transcription regulating domain comprises a nuclear hormone receptor transcription activation domain or variant thereof that has transcription activation activity.
17. The fusion protein of claim 14, wherein the transcription regulating domain comprises a steroid hormone receptor transcription activation domain or variant thereof.
18. The fusion protein of claim 14, wherein the transcription regulating domain comprises a viral transcription activation domain or variant thereof that has transcription activation activity.
19. The fusion protein of claim 18, wherein the transcription regulating domain comprises a VP16 transcription activation domain or variant thereof.
21. The fusion protein of claim 20, wherein the transcription repression domain is selected from the group consisting of ERD, KRAB, SID, Deacetylase, and derivatives, multimers and combinations thereof

**Analysis**

It is evident from the disclosure in the application as of the earliest priority date that applicant had possession of each element as claimed in the rejected claims. Contrary to the assertion of the Examiner, Applicant has identified and taught how to modify each components of the fusion protein. Furthermore the LBD and TRD and variations thereof are known to those of skill in the art as are zinc fingers. The application spends pages describing zinc fingers, how to modify and select and prepare variants and combinations thereof. In addition, the specification provides a working Example (Example 1) demonstrating how variant zinc fingers for unique addressing can be identified and combined. There can be no doubt that applicant had possession of the claimed subject matter.

**A. The teachings in the specification**

Each of the rejected claim recites an element of the claimed fusion proteins and a variant thereof. As discussed below, the particular elements, LDB and TRD, and variants thereof are known and also are described in the application. Zinc finger modules are well known, and the application provides exquisite detail regarding combining the modules to address the ligand activated transcriptional regulator proteins. The application teaches that modified modules can be prepared, and describes how to do so, and combined for the purpose of addressing the fusion proteins. The specification (page 27) defines a variant as:

As used herein, a polypeptide "variant" or "derivative " refers to a polypeptide that is a mutagenized form of a polypeptide or one produced through recombination but that still retains a desired activity, such as the ability to bind to a ligand or a nucleic acid molecule or to modulate transcription.

Hence, as described in the specification, one only has to modify the particular element and test it to ensure that it retains a desired activity. It is clear that variants of each element are contemplated, since such are described (see, e.g., the definition reproduced below, of zinc finger variants. Hence, it is apparent that applicant appreciated and possession of each element at the time of the earliest priority date.

The instant specification provides fusion proteins containing zinc finger peptide nucleotide binding domains operatively linked to ligand binding domains derived from an intracellular receptor that may further comprise an operatively linked transcription regulating domain. The specification provides extensive lists of examples of each domain and exemplifies preparation of various fusion proteins having the structural and functional limitations as claimed. There is nothing of record that suggest applicant did not contemplate a fusion protein containing a ligand binding domain derived from an intracellular receptor, a DNA binding domain that is a zinc finger peptide assembled from modular units that specifically recognize 3 nucleotide sequences, and a transcription regulation domain. Moreover, the specification clearly sets forth the types of variants in each domain that would satisfy the structural and functional limitations of the claims.

Furthermore, each element of the fusion protein, the zinc finger domains, the LBDs and the optional TRDs are known as are variants thereof. The application is directed to the use of at least zinc finger domain modules to uniquely address ligand activated transcriptional regulator proteins. The application describes each element, including variants in great detail, with particular description focused on combining zinc finger modules for addressing. The following discussion provides exemplary disclosure from the specification and also shows that at the time of earliest claimed priority date, those of skill in the art were well-acquainted with each element and variants thereof.

The specification exemplifies in great detail the construction and expression of the claimed fusion genes, assays that screen for variants that fall within the scope of the claims by measuring specific binding of each of the domains, and assays to measure their potential as regulators of gene expression. As discussed above, the classes of molecules belonging to each of the domains of the instantly claimed fusion proteins had been characterized in exquisite detail in the art as of the effective filing date of the instant application and have also been extensively described in the specification so as to be adequately descriptive of "variants" that fall within the scope of the claims. Furthermore, as is well known to those of skill in the art (*see above*), and as described extensively in the specification, recombinant technology and binding assays may be uniformly applied to any or all of the molecules described in the specification due to their common structural and functional characteristics such as their target recognition sites, the structural motifs that create the specificity of recognition, and methods by which their ligand binding characteristics may be altered.

The ligand binding domain and variants thereof that would fall within the scope of the claims are described extensively at, for example, page 32, line 7 to page 33, line 11 of the specification, which provides methods, known to those of skill in the art, to prepare and characterize variants of the ligand binding domain, including specific changes that will provide altered endogenous or exogenous ligand specificity as desired. Page 33, line 12 to page 50, line 2 of the specification provides in exquisite detail and incorporates by reference what was known to those of skill in the art at the time of filing of the application concerning zinc finger proteins, the modular nature of zinc finger proteins wherein each zinc finger specifically recognizes a 3 nucleotide sequence, the types of zinc finger proteins, specific changes that provide variant zinc finger peptides that retain the characteristics of recognizing zinc finger DNA binding motifs, the rules for constructing, isolating or synthesizing such

variants, and how to screen for such variants. Page 50, line 3 to page 52, line 5 of the specification describes known transcriptional regulatory domains and selection and modifications thereof. At, for example, page 31, line 6, to page 32, line 6, the specification describes how to construct the claimed fusion proteins from the various domains and their variants. In addition, numerous working examples, discussed above, are provided throughout the specification, as are exemplary fusion proteins, encoded by SEQ ID NOS. 1-18. As described above, the working examples also set forth in great detail the construction and screening of variants that fall within the scope of the instant claims

For example, Page 32, line 7 to page 33, line 11 of the specification states:

**1. Ligand Binding Domain (LBD)**

The ligand binding domain is derived from an intracellular receptor, and is preferably derived from a nuclear hormone receptor. The LBD of an intracellular receptor includes the approximately 300 amino acids from the carboxy terminal, which can be used with or without modification. By mutation of a small number of residues ligand specificity can be altered. The ligand binding domain can be modified, such as by truncation or point mutation to alter its ligand specificity permitting gene regulation by non-natural or non-native ligands.

Exemplary hormone receptors are steroid receptors, which are well known in the art. Exemplary and preferred steroid receptors include estrogen and progesterone receptors and variants thereof. Of particular interest are ligand binding domains that exhibit altered ligand specificity so that the LBD does not respond to the natural hormone, but rather to a drug, such as RU486, or other inducer. **Means to modify and test the specificity of ligand binding domains and to identify ligands therefor are known (see, U.S. Patent No. 5,874,534; U.S. Patent No. 5,935,934; and International PCT application No. 98/18925, which is based on U.S. provisional application Serial No. 0/029,964; International PCT application No. 96/40911, which is based on U.S. application Serial No. 08/479,913).**

**The LBD can be modified by deletion of from about 1 up to about 150, typically 120, amino acids on the carboxyl terminal end of the receptor from which the LBD derives.** Systematic deletion of amino acids and subsequent testing of the ligand specificity and of the resulting LBD can be used to empirically identify mutations that lead to modified LBDs that have desired properties, such as preferential interaction with non-natural ligands. Exemplary mutations are described in the Examples herein, and also are known to those of skill in the art (see, *e.g.*, U.S. Patent No. 5,874,534; U.S. Patent No. 5,935,934; U.S. Patent No. 5,364,791; and International PCT application No. 98/18925, which is based on U.S. provisional application Serial No. 60/029,964; International PCT application No. 96/40911, which is based on U.S. application Serial No. 08/479,913) and references cited therein. **Hence a LBD or modified form thereof prepared by known methods is**

**obtained and operably linked to a DBD; a TRD is also linked as needed.**  
(emphasis added).

## **2. Zinc Finger modules and variants thereof**

The specification describes zinc fingers, modules and variations thereof, including synthetic and modified zinc fingers in extensive detail. The specification teaches how to modify zinc fingers and to identify variants. Exemplary variants are provided in Example 1.

At page 26, the specification defines a zinc finger variant:

As used herein, a zinc finger-nucleotide binding polypeptide "variant" or "derivative" refers to a polypeptide that is a mutagenized form of a zinc finger protein or one produced through recombination. A variant may be a hybrid that contains zinc finger domain(s) from one protein linked to zinc finger domain(s) of a second protein, for example. The domains may be wild type or mutagenized. A "variant" or "derivative" includes a truncated form of a wild type zinc finger protein, which contains less than the original number of fingers in the wild type protein. Examples of zinc finger-nucleotide binding polypeptides from which a derivative or variant may be produced include TFIIIA and zif268. Similar terms are used to refer to "variant" or "derivative" nuclear hormone receptors and "variant" or "derivative" transcription effector domains.

Furthermore, the specification provides great detail describing zinc fingers, modules thereof, modification thereof, how to identify variants and how to address the ligand activated fusion proteins. For example, at page 33, lines 15-29 of the specification states:

Zinc fingers are ubiquitous proteins, and many are well-characterized. **For example, methods and rules for preparation and selection of zinc fingers based upon the C2H2 class of zinc fingers with unique specificity are known** (see, e.g., International PCT application No. WO 98/54311 and International PCT application No. 95/19431; see, also U.S. Patent No. 5,789,538; Beerli *et al.* (1999) *Proc. Natl. Acad. Sci. U.S.A.* 96:2758-2763; Beerli *et al.* (1995) *Proc. Natl. Acad. Sci. U.S.A.* 95:14628-14633; see, also U.S. application Serial No. 09/173,941, filed 16 October, 1998, published as International PCT application No. WO 00/23464). Exemplary targeting sequences are provided herein.

**Furthermore, other zinc fingers can be similarly identified and the rules known for the C2H2 can be applied to modification of the specificity of such zinc fingers or alternative rules unique to each class can be deduced in a similar manner.** (emphasis added).

Further, at page 34, lines 16-30:

**For example, zinc finger variants can be prepared by identifying a zinc finger or modular unit thereof, creating an expression library, such as a phage display library** (see, *e.g.*, International PCT application No. WO 98/54311, Barbas *et al.* (1991) *Methods* 2:119; Barbas *et al.* (1992) *Proc. Natl. Acad. Sci. U.S.A.* 89:4457), encoding polypeptide variants of the zinc finger or modular unit thereof, expressing the library in a host and screening for variant peptides having a desired specificity. Zinc fingers may also be constructed by combining amino acids (or encoding nucleic acids) according to the known rules of binding specificity and, if necessary, testing or screening the resulting peptides to ensure the peptide has a desired specificity. **Because of the modular nature of zinc fingers, where each module can be prepared to bind to three nucleotides peptides of any specificity can be prepared from the modules.** The number of modules used depends upon the specificity of gene targeting desired. (emphasis added). **Example 1 at page 67 of the specification provides a number of zinc finger variants** produced in the manner described throughout the specification.

Continuing at pages 36-38, the specification describes how to design zinc finger addresses:

Studies of natural zinc finger proteins have shown that three zinc finger domains can bind 9 bp of contiguous DNA sequence (Pavletich *et al.* (1991) *Science* 252:809-817; Swirnoff *et al.* (1995) *Mol. Cell. Biol.* 15:2275-2287). While recognition of 9 bp of sequence is insufficient to specify a unique site in a complex genome, proteins containing six zinc finger domains can specify 18-bp recognition (Liu *et al.* (1997) *Proc. Natl. Acad. Sci. USA* 94:5525-5530). An 18-bp address made up of modular units is of sufficient complexity to specify a single site within all known genomes (see, published International PCT application No. WO 98/54311). Rules for constructing Zinc finger arrays that bind to a particular DNA sequence are known (see, *e.g.*, International PCT application No. WO 98/54311, which is based on U.S. application Serial No. 08/863,813; International PCT application No. 95/19431, which is based on U.S. application Serial Nos. 08/183,119 and 08/312,604).

Zinc finger-nucleotide binding polypeptide variants can be constructed from known motifs. The variants include at least two and preferably at least about four zinc finger modules that bind to a cellular nucleotide sequence, such as DNA, RNA or both, and specifically bind to and modulate the function of a cellular nucleotide sequence.

For purposes herein, it is not necessary that the zinc finger-nucleotide binding motif be known in order to obtain a zinc-finger nucleotide binding variant polypeptide. It is contemplated that zinc finger-nucleotide binding motifs can be identified in non-eukaryotic DNA or RNA, especially in the native promoters of bacteria and viruses by the binding thereto of the modified nucleic acid binding peptides. Modified nucleic acid binding peptides should preserve the well known structural characteristics of the zinc finger, but differ

from zinc finger proteins found in nature by their amino acid sequences and three-dimensional structures.

A variety of zinc finger proteins are known. Among these, the Cys<sub>2</sub>-His<sub>2</sub> (also referred to as "C2H2") zinc fingers are preferred for use in the fusion proteins. There are well-defined rules for C2H2 zinc finger binding to DNA that allow the DNA binding specificity of the fusion proteins containing the zinc fingers to be adjusted in order to reduce non-specific interactions with genes other than the targeted genes. These proteins can be selected or engineered to bind to diverse sequences. Further, the sequence specificity of these proteins can be modified to be different from their naturally occurring targets. Examples of zinc finger proteins from which a polypeptide can be produced include TFIIIA and Zif268.

The murine Cys<sub>2</sub>-His<sub>2</sub> zinc finger protein Zif268 has been used for construction of phage display libraries (Wu *et al.* (1995) *Proc. Natl. Acad. Sci. U.S.A.* 92:344-348). Zif268 is structurally the most well characterized of the zinc-finger proteins (Pavletich, *et al.* (1991) *Science* 252:809-817; Elrod-Erickson *et al.* (1996) *Structure* 4:1171-1180; Swirnoff *et al.* (1995) *Mol. Cell. Biol.* 15:2275-2287). DNA recognition in each of the three zinc finger domains of this protein is mediated by residues in the N-terminus of the  $\alpha$ -helix contacting primarily three nucleotides on a single strand of the DNA. The operator binding site for this three finger protein is 5'-GCGTGGGGCG-3' (finger-2 subsite is underlined). Structural studies of Zif268 and other related zinc finger-DNA complexes have shown that residues from primarily three positions on the  $\alpha$ -helix, -1, 3, and 6, are involved in specific base contacts. Typically, the residue at position -1 of the  $\alpha$ -helix contacts the 3' base of that finger's subsite while positions 3 and 6 contact the middle base and the 5' base, respectively.

### **(3) The TRD and variants thereof**

The specification provides great detail describing TRDs and variants thereof and how to make variants. For example, at page 50, lines 13-18 of the specification states:

#### **Selection of the TRD**

Transcription regulating domains are well known in the art. Exemplary and preferred transcription repressor domains are ERD, KRAB, SID, Deacetylase, and derivatives, multimers and combinations thereof such as KRAB-ERD, SID-ERD, (KRAB)<sub>2</sub>, (KRAB)<sub>3</sub>, KRAB-A, (KRAB-A)<sub>2</sub>, (SID)<sub>2</sub> (KRAB-A)-SID and SID-(KRAB-A).

Thus each element of the claimed fusion proteins described in the specification, including modifications thereof and variations thereof. As note, while the concept of using zinc finger domain modules to uniquely address the ligand activated transcriptional regulator proteins; each claimed element and variations thereof is known and/or taught in great detail in the specification. Zinc finger modules are known, and the specification teaches how to combine them to create unique addresses.

**B. The knowledge of those of skill in the art**

Furthermore, those of skill in the art have familiarity with each of the elements and variants thereof, so that they can be combined as claimed and described in the application and in the priority application.

As discussed above, the written description can be satisfied by the disclosure of identifying characteristics, including structural and physical characteristics, or functional characteristics coupled with a known or disclosed correlation with structural characteristics, or a combination of such factors sufficient to demonstrate that the applicant was in possession of the claimed subject matter. MPEP § 2163; see *University of California v. Eli Lilly*, 119 F.3d 1559, 1568, 43 USPQ2d 1398, 1406 (Fed. Cir. 1997). Further, as noted above, the standard is an objective one, based on what one of skill in the art would recognize in the disclosure. In *re Gosteli*, 872 F.2d at 1012. Thus, the knowledge and level of skill in the art is a factor to be considered in determining the standard. It is not necessary to include in the specification that which those of skill in the art know; the specification is presumed to include all such knowledge.

The instant claims are drawn to fusion proteins containing a nucleotide binding domain linked to a modified ligand binding domain and, in some embodiments, further linked to a transcription regulating domain, including variants thereof. The components of the claimed fusion proteins, namely, the nucleotide binding domain, the modified ligand binding domain and the transcription regulating domain were well-known and had been extensively characterized in terms of their sequence, structure, function and mechanism of action. Further, sequence variants of these domains, and the effects of such sequence variation on the functions of these domains, were well-known to those of skill in the art as of this application's earliest priority date (October 1999). Thus, in light of the description provided herein and the knowledge of those of skill in the art, Applicant clearly was in possession of the genus of fusion proteins as claimed herein, including fusion proteins containing: (1) variants of zinc finger proteins; (2) variants of a nuclear hormone receptor transcription activation domain; (3) variants of the LBD domains of the progesterone receptor other than the progesterone variants disclosed in Table 10; (4) variants of the estrogen receptor other than those described at page 125, lines 8-10 of the specification; (5) derivatives, multimers and combinations of VP16, VP64, TA2, STAT-6 or p65; and (5) derivatives, multimers and

combinations of the transcription repression domain other than KRAB-ERD, SID-ERD, (KRAB)2, (KRAB)3, (SID)2, (KRAB-A)-SID and SID-(KRAB-A).

For example, at the time the instant application was filed and as of its earliest priority date, ligand binding domains (LBDs), including nuclear hormone receptors such as estrogen and progesterone receptors, had extensively been characterized in terms of their sequence, their function, and the correlation between particular variations in sequence and the resulting impact on function. For example, several publications describe estrogen and progesterone receptor sequence variants and their correlation with function, including: (1) Graham et al., *Cancer Res.*, 50:6208-6217, (1990), which describes mutations in the estrogen receptor that influence its ability to bind to its cognate ligand (estrogen); (2) Fuqua et al., *Cancer Res.*, 52:483-486 (1992), directed to a truncated estrogen receptor variant that inhibits the binding of wild-type estrogen receptor to its cognate ligand; (3) Hodges et al., *Circulation*, 99:2688-2693 (May 1999), which describes numerous variants of the estrogen and progesterone receptors and their effect on functional characteristics including hormone binding and transcription regulation; (4) Taylor et al., *Nucl. Acids Res.*, 20:2895 (1992), which describes an estrogen receptor sequence variant in the region that modulates transcription activation; (5) Leygue et al., *Cancer Res.*, 56:4324-4327 (1996), which describes numerous estrogen receptor variants and their role in human breast cancer; (6) Fuqua et al., *J. Cell. Biochem. Suppl.* 17G:194-197 (1993), which is a study of several estrogen receptor variants, including one variant that has a truncation within the hormone binding domain, resulting in the loss of hormone binding ability; (7) Fuqua et al., *Cancer Res.*, 51:105-109 (1991), which describes estrogen receptor variants having altered hormone binding and/or transcriptional activities; and (8) Balleine et al., *J. Clin. Endocrin. Metab.*, 84:1370-1377 (April 1999), which describes alternatively spliced estrogen and progesterone receptor variants and their effect in human breast cancer.

With respect to the zinc finger variants, as discussed above, the specification provides extensive details regarding the sequence, structure and DNA binding features of zinc finger domains, including zinc finger variants, such as mutants and synthetic zinc fingers and how to prepare variants that uniquely address genes.. The specification further provides methods for identifying, modifying or synthesizing zinc finger domains to obtain nucleic acid binding domains of desired specificity and/or affinity. Furthermore, as the specification describes, zinc finger domains and their variants were well-known and extensively studied in the art as

of the instant application's earliest priority date. For example, methods and rules for preparation and selection of zinc fingers with unique specificity are described in International PCT application No. WO 98/54311 and International PCT application No. 95/19431; see, also U.S. Patent No. 5,789,538; Beerli et al. (1999) Proc. Natl. Acad. Sci. U.S.A. 96:2758-2763; Beerli et al. (1995) Proc. Natl. Acad. Sci. U.S.A. 95:14628-14633. Rules for creating zinc fingers of desired specificity also were known (see, e.g., (see, e.g., International PCT application No. WO 98/54311; International PCT application No. WO 95/19431).

Further, at the time the instant application was filed and as of its earliest priority date, the sequence, structure, function and mechanism of action of transcription activation domains and transcription repressor domains was well-known, as was the relationship among the aforementioned parameters. As was recognized long before the instant application's earliest priority date, transcription activator domains are readily interchangeable between proteins, including proteins of different species, and can be dimerized or multimerized in any combination to work cooperatively and provide the level and/or type of transcriptional regulation desired (Ptashne, Nature, 335:683-689 (1988). The same publication (Ptashne) also describes sequence variations (mutations) that can convert transcription repressors into transcription activators. Other publications describe the versatility of transcription regulation domains, including their ability to retain or even enhance their activity by dimerization or multimerization in various combinations (see, e.g., Mendel et al., Science, 254:1762-1767 (1991); Mitchell et al., Science, 245:371-378 (1989); and Landschultz et al., Science, 240:1759-1764 (1988)).

Several publications have described and extensively characterized regions of transcription regulation domains that are responsible for particular functions, such as nuclear localization, transactivation, DNA binding and multimerization. For example, the TA1, TA2 and p65 transcription activation domains and variants thereof have extensively been characterized, as evidenced by the following publications: Schmitz et al., J. Biol. Chem., 270:15576-15584 (1995); Ganchi et al., Mol. Cell. Biol., 13:7826-7835 (1993); Ruben et al., Mol. Cell. Biol., 12:444-454 (1992); Pappetrou et al., J. Med. Genet., 36:208-213 (March 1999); Perkins et al., Proc. Natl. Acad. Sci. USA, 89:1529-1533 (1992); and Ledebur et al., J. Biol. Chem., 270:933-943 (1995). Benbrook et al., Nucl. Acids Res., 22:1463-1469 (1994) and Pazin et al., J. Biol. Chem., 273:34653-34660 (1998) describe heterodimers of VP16 with other transcriptional regulators, such as CREB and GAL4. Further, Shaw et al., J. Biol.

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Chem., 270:29030-29037 (1995), describes and extensively characterizes sequence variations in VP16, and the resulting impact on function

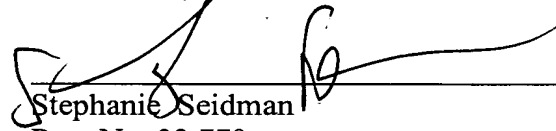
**Conclusion**

Based on the disclosure of the specification as well as the knowledge of those of skill in the art at the time that the application was filed, it is evident that applicant was in possession of each element of the rejected claims as claimed. This rejection cannot be sustained.

\* \* \*

In view of the above, examination of the application on the merits and allowance are respectfully requested.

Respectfully submitted,

  
Stephanie Seidman  
Reg. No. 33,779

Attorney Docket No. 17083-003002/1227B

**Address all correspondence to:**

Stephanie L. Seidman  
Fish & Richardson P.C.  
12390 El Camino Real  
San Diego, California 92130  
Telephone: (858) 678-4777  
Facsimile: (202) 626-7796  
email: [seidman@fr.com](mailto:seidman@fr.com)